Galvus

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Galvus 50 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of vildagliptin.

Excipient: Each tablet contains 47.82 mg anhydrous lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White to light yellowish, round (8 mm diameter), flat-faced, bevelled-edge tablet. One side is debossed with "NVR", and the other side with "FB".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vildagliptin is indicated in the treatment of type 2 diabetes mellitus:

As dual oral therapy in combination with
- metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin,
- a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance,
- a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate.

4.2 Posology and method of administration

Adults
When used in dual combination with metformin or a thiazolidinedione, the recommended daily dose of vildagliptin is 100 mg.

The 100 mg dose may be administered either once daily in the morning or divided into two doses of 50 mg given in the morning and in the evening.

When used in dual combination with a sulphonylurea, the recommended dose of vildagliptin is 50 mg once daily administered in the morning. In this patient population, vildagliptin 100 mg daily was no more effective than vildagliptin 50 mg once daily.

Doses higher than 100 mg are not recommended.

The safety and efficacy of vildagliptin as triple oral therapy in combination with metformin and a thiazolidinedione or with metformin and a sulphonylurea has not been established.

Galvus can be administered with or without a meal (see also section 5.2).

Additional information on special populations

Renal impairment

No dose adjustment is required in patients with mild renal impairment (creatinine clearance ≥ 50 ml/min). The use of Galvus is not recommended in patients with moderate or severe renal impairment or in haemodialysis patients with end-stage renal disease (ESRD) (see also sections 4.4 and 5.2).

Hepatic impairment

No dose adjustment is required in patients with mild to moderate hepatic impairment. The use of Galvus is not recommended in patients with severe hepatic impairment (see also sections 4.4 and 5.2).

Elderly (≥ 65 years)

No dose adjustments are necessary in elderly patients. Experience in patients aged 75 years and older is limited and caution should be exercised when treating this population (see also sections 5.1 and 5.2).

Paediatric population (< 18 years)

Galvus is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

General

Galvus is not a substitute for insulin in insulin-requiring patients. Galvus should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Renal impairment

There is limited experience in patients with moderate to severe renal impairment or in patients with ESRD on haemodialysis. Therefore, the use of Galvus is not recommended in these patients.

Liver enzyme monitoring

A small numerical imbalance of reports of generally asymptomatic elevated transaminases was reported in patients treated with vildagliptin 100 mg daily in controlled clinical trials (see section 4.8). Therefore, as per routine clinical practice, it is recommended that liver function tests be performed prior to the initiation of treatment with Galvus in order to know the patient's baseline value and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return(s) to normal. Should an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) of 3x the upper limit of normal (ULN) or greater persist, withdrawal of Galvus therapy is recommended.

Galvus should not be used in patients with severe hepatic impairment.

Cardiac failure

Experience with vildagliptin therapy in patients with congestive heart failure of New York Heart Association (NYHA) functional class I-II is limited and therefore vildagliptin should be used cautiously in these patients. There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class III-IV and therefore use is not recommended in these patients.

Skin disorders

Skin lesions, including blistering and ulceration have been reported in extremities of monkeys in non-clinical toxicology studies (see section 5.3). Although skin lesions were not observed at an increased incidence in clinical trials, there was limited experience in patients with diabetic skin complications.

Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering or ulceration, is recommended.

Excipients
The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Vildagliptin has a low potential for interactions with co-administered medicinal products. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate and does not inhibit or induce CYP 450 enzymes, it is not likely to interact with active substances that are substrates, inhibitors or inducers of these enzymes.

Combination with pioglitazone, metformin and glyburide
Results from studies conducted with these oral antidiabetics have shown no clinically relevant pharmacokinetic interactions.

Digoxin (Pgp substrate), warfarin (CYP2C9 substrate)
Clinical studies performed with healthy subjects have shown no clinically relevant pharmacokinetic interactions. However, this has not been established in the target population.

Combination with amlodipine, ramipril, valsartan or simvastatin
Drug-drug interaction studies in healthy subjects were conducted with amlodipine, ramipril, valsartan and simvastatin. In these studies, no clinically relevant pharmacokinetic interactions were observed after co-administration with vildagliptin.

As with other oral antidiabetic medicinal products the hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics.

4.6 Pregnancy and lactation

There are no adequate data from the use of vildagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). The potential risk for humans is unknown. Due to lack of human data, Galvus should not be used during pregnancy.

It is not known whether vildagliptin is excreted in human breast milk. Animal studies have shown excretion of vildagliptin in milk. Galvus should not be used during lactation.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients who experience dizziness as an undesirable effect should avoid driving vehicles or using machines.

4.8 Undesirable effects

Safety data were obtained from a total of 3,784 patients exposed to vildagliptin at a daily dose of 50 mg (once daily) or 100 mg (50 mg twice daily or 100 mg once daily) in controlled trials of at least 12 weeks duration. Of these patients, 2,264 patients received vildagliptin as monotherapy and 1,520 patients received vildagliptin in combination with another medicinal product. 2,682 patients were treated with vildagliptin 100 mg daily (either 50 mg twice daily or 100 mg once daily) and 1,102 patients were treated with vildagliptin 50 mg once daily.

The majority of adverse reactions in these trials were mild and transient, not requiring treatment discontinuations. No association was found between adverse reactions and age, ethnicity, duration of exposure or daily dose.

Rare cases of angioedema have been reported on vildagliptin at a similar rate to controls. A greater proportion of cases were reported when vildagliptin was administered in combination with an angiotensin converting enzyme inhibitor (ACE-Inhibitor). The majority of events were mild in severity and resolved with ongoing vildagliptin treatment.

Adverse reactions reported in patients who received Galvus in double-blind studies as monotherapy and add-on therapies are listed below for each indication by system organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Combination with metformin

In controlled clinical trials with the combination of vildagliptin 100 mg daily + metformin, no withdrawal due to adverse reactions was reported in either the vildagliptin 100 mg daily + metformin or the placebo + metformin treatment groups.

In clinical trials, the incidence of hypoglycaemia was uncommon in patients receiving vildagliptin 100 mg daily in combination with metformin (1%) and in patients receiving placebo + metformin (0.4%). No severe hypoglycaemic events were reported in the vildagliptin arms.

In clinical trials, weight did not change from baseline when vildagliptin 100 mg daily was added to metformin (+0.2 kg and -1.0 kg for vildagliptin and placebo, respectively).

Table 1 Adverse reactions reported in patients who received Galvus 100 mg daily in combination with metformin in double-blind studies (N=208)

Nervous system disorders	
Common	Tremor
Common	Headache
Common	Dizziness
Uncommon	Fatigue
Gastrointestinal disorders	
Common	Nausea

Combination with a sulphonylurea

In controlled clinical trials with the combination of vildagliptin 50 mg + a sulphonylurea, the overall incidence of withdrawals due to adverse reactions was 0.6% in the vildagliptin 50 mg + sulphonylurea vs 0% in the placebo + sulphonylurea treatment group.

In clinical trials, the incidence of hypoglycaemia when vildagliptin 50 mg once daily was added to glimepiride was 1.2% versus 0.6% for placebo + glimepiride. No severe hypoglycaemic events were reported in the vildagliptin arms.

In clinical trials, weight did not change from baseline when vildagliptin 50 mg daily was added to glimepiride (-0.1 kg and -0.4 kg for vildagliptin and placebo, respectively).

Table 2 Adverse reactions reported in patients who received Galvus 50 mg in combination with a sulphonylurea in double-blind studies (N=170)

Infections and infestations	
Very rare	Nasopharyngitis
Nervous system disorders	
Common	Tremor
Common	Headache
Common	Dizziness

Gastrointestinal disorders	
Uncommon	Constipation
General disorders and administration site conditions	
Common	Asthenia

Combination with a thiazolidinedione
In controlled clinical trials with the combination of vildagliptin 100 mg daily+ a thiazolidinedione, no withdrawal due to adverse reactions was reported in either the vildagliptin 100 mg daily + thiazolidinedione or the placebo + thiazolidinedione treatment groups.

In clinical trials, the incidence of hypoglycaemia was uncommon in patients receiving vildagliptin + pioglitazone (0.3%) but common in patients receiving placebo + pioglitazone (1.9%). No severe hypoglycaemic events were reported in the vildagliptin arms.

In the pioglitazone add-on study, the absolute weight increases with placebo, Galvus 100 mg daily were 1.4 and 2.7 kg, respectively.

The incidence of peripheral oedema when vildagliptin 100 mg daily was added to a maximum dose of background pioglitazone (45 mg once daily) was 7.0%, compared to 2.5% for background pioglitazone alone.

Table 3 Adverse reactions reported in patients who received Galvus 100 mg daily in combination with a thiazolidinedione in double-blind studies (N=158)

Nervous system disorder	
Uncommon	Headache
Uncommon	Asthenia
Metabolism and nutrition disorders	
Common	Weight increase
Vascular disorders	
Common	Oedema peripheral

In addition, in controlled monotherapy trials with vildagliptin 100 mg daily, adverse reactions reported in patients treated with vildagliptin in excess of that in patients receiving placebo are dizziness, headache, oedema peripheral, constipation, nasopharyngitis, upper respiratory tract infection and arthralgia. In these trials, the overall incidence of withdrawals due to adverse reactions was no greater for patients treated with vildagliptin at doses of 100 mg daily (0.3%) than for placebo (0.6%) or comparators (0.9%).

In comparative controlled monotherapy studies, hypoglycaemia was uncommon, reported in 0.4% (7 of 1,855) of patients treated with vildagliptin 100 mg daily compared to 0.2% (2 of 1,082) of patients in the groups treated with an active comparator or placebo, with no serious or severe events reported.

In controlled monotherapy trials of up to one year in duration, the incidence of ALT or AST elevations > 3x ULN (classified as present on at least 2 consecutive measurements or at the final on-treatment visit) was 0.3%, 0.9% and 0.3% for vildagliptin 50 mg once daily, vildagliptin 100 mg daily (administered as single and divided doses) and placebo, respectively. These elevations in transaminases were generally asymptomatic, non-progressive in nature and not associated with cholestasis or jaundice.

In clinical trials, weight did not change from baseline when vildagliptin 100 mg daily was administered as monotherapy (-0.3 kg and -1.3 kg for vildagliptin and placebo, respectively).

4.9 Overdose

Information regarding overdose with vildagliptin is limited.

Information on the likely symptoms of overdose was taken from a rising dose tolerability study in healthy subjects given Galvus for 10 days. At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paraesthesia, fever, oedema and a transient increase in lipase levels. At 600 mg, one subject experienced oedema of the feet and hands, and increases in creatine phosphokinase (CPK), aspartate aminotransferase (AST), C-reactive protein (CRP) and myoglobin levels. Three other subjects experienced oedema of the feet, with paraesthesia in two cases. All symptoms and laboratory abnormalities resolved without treatment after discontinuation of the study medicinal product.

Management
In the event of an overdose, supportive management is recommended. Vildagliptin cannot be removed by haemodialysis. However, the major hydrolysis metabolite (LAY 151) can be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dipeptidyl peptidase 4 (DPP-4) inhibitors, ATC code: A10BH02

Vildagliptin, a member of the islet enhancer class, is a potent and selective DPP-4 inhibitor.

The administration of vildagliptin results in a rapid and complete inhibition of DPP-4 activity, resulting in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide).

By increasing the endogenous levels of these incretin hormones, vildagliptin enhances the sensitivity of beta cells to glucose, resulting in improved glucose-dependent insulin secretion. Treatment with vildagliptin 50-100 mg daily in patients with type 2 diabetes significantly improved markers of beta cell function including HOMA-β (Homeostasis Model Assessment–β), proinsulin to insulin ratio and measures of beta cell responsiveness from the frequently-sampled meal tolerance test. In non-diabetic (normal glycaemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.

By increasing endogenous GLP-1 levels, vildagliptin also enhances the sensitivity of alpha cells to glucose, resulting in more glucose-appropriate glucagon secretion.

The enhanced increase in the insulin/glucagon ratio during hyperglycaemia due to increased incretin hormone levels results in a decrease in fasting and postprandial hepatic glucose production, leading to reduced glycaemia.

The known effect of increased GLP-1 levels delaying gastric emptying is not observed with vildagliptin treatment.

A total of 5,759 patients with type 2 diabetes participated in 13 double-blind placebo- or active-controlled clinical trials of at least 12-weeks' treatment duration. In these studies, vildagliptin was administered to 3,784 patients at daily doses of 50 mg (once daily) or 100 mg (50 mg twice daily or 100 mg once daily). The number of male and female patients receiving vildagliptin 50 mg once daily or 100 mg daily was 2,069 and 1,715, respectively. The number of patients receiving vildagliptin 50 mg once daily or 100 mg daily who were $\geq$ 65 years of age was 664 and 121 of the patients were $\geq$ 75 years of age. In these trials, vildagliptin was administered as monotherapy in drug-naïve patients with type 2 diabetes or in combination in patients not adequately controlled by other antidiabetic medicinal products.

Overall, vildagliptin improved glycaemic control when given as monotherapy or when used in combination with metformin, a sulphonylurea, and a thiazolidinedione, as measured by clinically relevant reductions in HbA_{1c} from baseline at study endpoint (see Table 4).

In clinical trials, the magnitude of HbA_{1c} reductions with vildagliptin was greater in patients with higher baseline HbA_{1c}.

In a 52-week double-blind controlled trial, vildagliptin (100 mg/day) reduced baseline HbA_{1c} by -1% compared to -1.6% for metformin (titrated to 2 g/day) statistical non-inferiority was not achieved. Patients treated with vildagliptin reported significantly lower incidences of gastrointestinal adverse reactions versus those treated with metformin.

In a 24-week double-blind controlled trial, vildagliptin (100 mg day) was compared to rosiglitazone (8 mg once daily). Mean reductions were -1.20% with vildagliptin and -1.38% with rosiglitazone in patients with mean baseline HbA_{1c} of 8.7%. Patients receiving rosiglitazone experienced a mean increase in weight (+1.6 kg) while those receiving vildagliptin experienced no weight gain (-0.3 kg). The incidence of peripheral oedema was lower in the vildagliptin group than in the rosiglitazone group (2.1% vs. 4.1% respectively).

Table 4 Key efficacy results of vildagliptin in placebo-controlled monotherapy trials and in add-on combination therapy trials (primary efficacy ITT population)

Monotherapy placebo controlled studies	**Mean baseline HbA_{1c} (%)**	**Mean change from baseline in HbA_{1c} (%) at week 24**	**Placebo-corrected mean change in HbA_{1c} (%) at week 24 (95%CI)**
Study 2301: Vildagliptin 50 mg twice daily (N=90)	8.6	-0.8	-0.5* (-0.8, -0.1)
Study 2301: Vildagliptin 100 mg once daily (N=92)	8.4	-0.9	-0.6* (-0.9, -0.2)
Study 2384: Vildagliptin 50 mg twice daily (N=79)	8.4	-0.7	-0.7* (-1.1, -0.4)
Study 2384: Vildagliptin 100 mg once daily (N=89)	8.3	-0.8	-0.9* (-1.2, -0.5)
		* p< 0.05 for comparison versus placebo	
Add-on / Combination studies			
Vildagliptin 100 mg daily + metformin (N=143)	8.4	-0.9	-1.1* (-1.4, -0.8)
Vildagliptin 50 mg daily + glimepiride (N=132)	8.5	-0.6	-0.6* (-0.9, -0.4)
Vildagliptin 100 mg daily + pioglitazone (N=136)	8.7	-1.0	-0.7* (-0.9, -0.4)
		* p< 0.05 for comparison versus placebo + comparator	

5.2 Pharmacokinetic properties

Absorption

Following oral administration in the fasting state, vildagliptin is rapidly absorbed, with peak plasma concentrations observed at 1.7 hours. Food slightly delays the time to peak plasma concentration to 2.5 hours, but does not alter the overall exposure (AUC). Administration of vildagliptin with food resulted in a decreased C_{max} (19%). However, the magnitude of change is not clinically significant, so that Galvus can be given with or without food. The absolute bioavailability is 85%.

Distribution

The plasma protein binding of vildagliptin is low (9.3%) and vildagliptin distributes equally between plasma and red blood cells. The mean volume of distribution of vildagliptin at steady-state after intravenous administration (V_{ss}) is 71 litres, suggesting extravascular distribution.

Biotransformation

Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69% of the dose. The major metabolite (LAY 151) is pharmacologically inactive and is the hydrolysis product of the cyano moiety, accounting for 57% of the dose, followed by the amide hydrolysis product (4% of dose). In vitro data in human kidney microsomes suggest that the kidney may be one of the major organs contributing to the hydrolysis of vildagliptin to its major inactive metabolite, LAY151. DPP-4 contributes partially to the hydrolysis of vildagliptin based on an *in vivo* study using DPP-4 deficient rats. Vildagliptin is not metabolised by CYP 450 enzymes to any quantifiable extent. Accordingly, the metabolic clearance of vildagliptin is not anticipated to be affected by co-medications that are CYP 450 inhibitors and/or inducers. *In vitro* studies demonstrated that vildagliptin does not inhibit/induce CYP 450 enzymes. Therefore, vildagliptin is not likely to affect metabolic clearance of co-medications metabolised by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 or CYP 3A4/5.

Elimination

Following oral administration of [^{14}C] vildagliptin, approximately 85% of the dose was excreted into the urine and 15% of the dose is recovered in the faeces. Renal excretion of the unchanged vildagliptin accounted for 23% of the dose after oral administration. After intravenous administration to healthy subjects, the total plasma and renal clearances of vildagliptin are 41 and 13 l/h, respectively. The mean elimination half-life after intravenous administration is approximately 2 hours. The elimination half-life after oral administration is approximately 3 hours.

Linearity / non-linearity

The C_{max} for vildagliptin and the area under the plasma concentrations versus time curves (AUC) increased in an approximately dose proportional manner over the therapeutic dose range.

Characteristics in patients

Gender

No clinically relevant differences in the pharmacokinetics of vildagliptin were observed between male and female healthy subjects within a wide range of age and body mass index (BMI). DPP-4 inhibition by vildagliptin is not affected by gender.

Age

In healthy elderly subjects (≥ 70 years), the overall exposure of vildagliptin (100 mg once daily) was increased by 32%, with an 18% increase in peak plasma concentration as compared to young healthy subjects (18-40 years). These changes are, however, not considered to be clinically relevant. DPP-4 inhibition by vildagliptin is not affected by age.

Hepatic impairment

The effect of impaired hepatic function on the pharmacokinetics of vildagliptin was studied in patients with mild, moderate and severe hepatic impairment based on the Child-Pugh scores (ranging from 6 for mild to 12 for severe) in comparison with healthy subjects. The exposure to vildagliptin after a single dose in patients with mild and moderate hepatic impairment was decreased (20% and 8%, respectively), while the exposure to vildagliptin for patients with severe impairment was increased by 22%. The maximum change (increase or decrease) in the exposure to vildagliptin is ~30%, which is not considered to be clinically relevant. There was no correlation between the severity of the hepatic disease and changes in the exposure to vildagliptin.

Renal impairment

In subjects with mild, moderate, or severe renal impairment, systemic exposure to vildagliptin was increased (C_{max} 8-66%; AUC 32-134%) and total body clearance was reduced compared to subjects with normal renal function.

Ethnic group

Limited data suggest that race does not have any major influence on vildagliptin pharmacokinetics.

5.3 Preclinical safety data

Intra-cardiac impulse conduction delays were observed in dogs with a no-effect dose of 15 mg/kg (7-fold human exposure based on C_{max}).

Accumulation of foamy alveolar macrophages in the lung was observed in rats and mice. The no-effect dose in rats was 25 mg/kg (5-fold human exposure based on AUC) and in mice 750 mg/kg (142-fold human exposure).

Gastrointestinal symptoms, particularly soft faeces, mucoid faeces, diarrhoea and, at higher doses, faecal blood were observed in dogs. A no-effect level was not established.

Vildagliptin was not mutagenic in conventional *in vitro* and *in vivo* tests for genotoxicity.

A fertility and early embryonic development study in rats revealed no evidence of impaired fertility, reproductive performance or early embryonic development due to vildagliptin. Embryo-foetal toxicity was evaluated in rats and rabbits. An increased incidence of wavy ribs was observed in rats in association with reduced maternal body weight parameters, with a no-effect dose of 75 mg/kg (10-fold human exposure). In rabbits, decreased foetal weight and skeletal variations indicative of developmental delays were noted only in the presence of severe maternal toxicity, with a no-effect dose of 50 mg/kg (9-fold human exposure). A pre- and postnatal development study was performed in rats. Findings were only observed in association with maternal toxicity at $\geq$ 150 mg/kg and included a transient decrease in body weight and reduced motor activity in the F1 generation.

A two-year carcinogenicity study was conducted in rats at oral doses up to 900 mg/kg (approximately 200 times human exposure at the maximum recommended dose). No increases in tumour incidence attributable to vildagliptin were observed. Another two-year carcinogenicity study was conducted in mice at oral doses up to 1,000 mg/kg. An increased incidence of mammary adenocarcinomas and haemangiosarcomas was observed with a no-effect dose of 500 mg/kg (59-fold human exposure) and 100 mg/kg (16-fold human exposure), respectively. The increased incidence of these tumours in mice is considered not to represent a significant risk to humans based on the lack of genotoxicity of vildagliptin and its principal metabolite, the occurrence of tumours only in one species and the high systemic exposure ratios at which tumours were observed.

In a 13-week toxicology study in cynomolgus monkeys, skin lesions have been recorded at doses $\geq$ 5 mg/kg/day. These were consistently located on the extremities (hands, feet, ears and tail). At 5 mg/kg/day (approximately equivalent to human AUC exposure at the 100 mg dose), only blisters were observed. They were reversible despite continued treatment and were not associated with histopathological abnormalities. Flaking skin, peeling skin, scabs and tail sores with correlating histopathological changes were noted at doses $\geq$ 20 mg/kg/day (approximately 3 times human AUC exposure at the 100 mg dose). Necrotic lesions of the tail were observed at $\geq$ 80 mg/kg/day. Skin lesions were not reversible in the monkeys treated at 160 mg/kg/day during a 4-week recovery period.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, anhydrous
Cellulose, microcrystalline
Sodium starch glycolate (type A)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium/Aluminium (PA/Al/PVC//Al) blister
Available in packs containing 7, 14, 28, 30, 56, 60, 90, 112, 180 or 336 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Galvus 100 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg of vildagliptin.

Excipient: Each tablet contains 95.64 mg anhydrous lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White to light yellowish, elongated (14 x 5.5 mm) tablet. One side is debossed with "NVR", and the other side with "HL".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vildagliptin is indicated in the treatment of type 2 diabetes mellitus:

As dual oral therapy in combination with
- metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin,
- a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance,
- a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate.

4.2 Posology and method of administration

Adults
When used in dual combination with metformin or a thiazolidinedione, the recommended daily dose of vildagliptin is 100 mg.

The 100 mg dose may be administered either once daily in the morning or divided into two doses of 50 mg given in the morning and in the evening.

When used in dual combination with a sulphonylurea, the recommended dose of vildagliptin is 50 mg once daily administered in the morning. In this patient population, vildagliptin 100 mg daily was no more effective than vildagliptin 50 mg once daily.

Doses higher than 100 mg are not recommended.

The safety and efficacy of vildagliptin as triple oral therapy in combination with metformin and a thiazolidinedione or with metformin and a sulphonylurea has not been established.

Galvus can be administered with or without a meal (see also section 5.2).

Additional information on special populations

Renal impairment

No dose adjustment is required in patients with mild renal impairment (creatinine clearance ≥ 50 ml/min). The use of Galvus is not recommended in patients with moderate or severe renal impairment or in haemodialysis patients with end-stage renal disease (ESRD) (see also sections 4.4 and 5.2).

Hepatic impairment

No dose adjustment is required in patients with mild to moderate hepatic impairment. The use of Galvus is not recommended in patients with severe hepatic impairment (see also sections 4.4 and 5.2).

Elderly (≥ 65 years)

No dose adjustments are necessary in elderly patients. Experience in patients aged 75 years and older is limited and caution should be exercised when treating this population (see also sections 5.1 and 5.2).

Paediatric population (< 18 years)

Galvus is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

General

Galvus is not a substitute for insulin in insulin-requiring patients. Galvus should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Renal impairment

There is limited experience in patients with moderate to severe renal impairment or in patients with ESRD on haemodialysis. Therefore, the use of Galvus is not recommended in these patients.

Liver enzyme monitoring

A small numerical imbalance of reports of generally asymptomatic elevated transaminases was reported in patients treated with vildagliptin 100 mg daily in controlled clinical trials (see section 4.8). Therefore, as per routine clinical practice, it is recommended that liver function tests be performed prior to the initiation of treatment with Galvus in order to know the patient's baseline value and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return(s) to normal. Should an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) of 3x the upper limit of normal (ULN) or greater persist, withdrawal of Galvus therapy is recommended.

Galvus should not be used in patients with severe hepatic impairment.

Cardiac failure

Experience with vildagliptin therapy in patients with congestive heart failure of New York Heart Association (NYHA) functional class I-II is limited and therefore vildagliptin should be used cautiously in these patients. There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class III-IV and therefore use is not recommended in these patients.

Skin disorders

Skin lesions, including blistering and ulceration have been reported in extremities of monkeys in non-clinical toxicology studies (see section 5.3). Although skin lesions were not observed at an increased incidence in clinical trials, there was limited experience in patients with diabetic skin complications.

Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering or ulceration, is recommended.

Excipients
The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Vildagliptin has a low potential for interactions with co-administered medicinal products. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate and does not inhibit or induce CYP 450 enzymes, it is not likely to interact with active substances that are substrates, inhibitors or inducers of these enzymes.

Combination with pioglitazone, metformin and glyburide
Results from studies conducted with these oral antidiabetics have shown no clinically relevant pharmacokinetic interactions.

Digoxin (Pgp substrate), warfarin (CYP2C9 substrate)
Clinical studies performed with healthy subjects have shown no clinically relevant pharmacokinetic interactions. However, this has not been established in the target population.

Combination with amlodipine, ramipril, valsartan or simvastatin
Drug-drug interaction studies in healthy subjects were conducted with amlodipine, ramipril, valsartan and simvastatin. In these studies, no clinically relevant pharmacokinetic interactions were observed after co-administration with vildagliptin.

As with other oral antidiabetic medicinal products the hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics.

4.6 Pregnancy and lactation

There are no adequate data from the use of vildagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). The potential risk for humans is unknown. Due to lack of human data, Galvus should not be used during pregnancy.

It is not known whether vildagliptin is excreted in human breast milk. Animal studies have shown excretion of vildagliptin in milk. Galvus should not be used during lactation.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients who experience dizziness as an undesirable effect should avoid driving vehicles or using machines.

4.8 Undesirable effects

Safety data were obtained from a total of 3,784 patients exposed to vildagliptin at a daily dose of 50 mg (once daily) or 100 mg (50 mg twice daily or 100 mg once daily) in controlled trials of at least 12 weeks duration. Of these patients, 2,264 patients received vildagliptin as monotherapy and 1,520 patients received vildagliptin in combination with another medicinal product. 2,682 patients were treated with vildagliptin 100 mg daily (either 50 mg twice daily or 100 mg once daily) and 1,102 patients were treated with vildagliptin 50 mg once daily.

The majority of adverse reactions in these trials were mild and transient, not requiring treatment discontinuations. No association was found between adverse reactions and age, ethnicity, duration of exposure or daily dose.

Rare cases of angioedema have been reported on vildagliptin at a similar rate to controls. A greater proportion of cases were reported when vildagliptin was administered in combination with an angiotensin converting enzyme inhibitor (ACE-Inhibitor). The majority of events were mild in severity and resolved with ongoing vildagliptin treatment.

Adverse reactions reported in patients who received Galvus in double-blind studies as monotherapy and add-on therapies are listed below for each indication by system organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Combination with metformin
In controlled clinical trials with the combination of vildagliptin 100 mg daily + metformin, no withdrawal due to adverse reactions was reported in either the vildagliptin 100 mg daily + metformin or the placebo + metformin treatment groups.

In clinical trials, the incidence of hypoglycaemia was uncommon in patients receiving vildagliptin 100 mg daily in combination with metformin (1%) and in patients receiving placebo + metformin (0.4%). No severe hypoglycaemic events were reported in the vildagliptin arms.

In clinical trials, weight did not change from baseline when vildagliptin 100 mg daily was added to metformin (+0.2 kg and -1.0 kg for vildagliptin and placebo, respectively).

Table 1 Adverse reactions reported in patients who received Galvus 100 mg daily in combination with metformin in double-blind studies (N=208)

Nervous system disorders	
Common	Tremor
Common	Headache
Common	Dizziness
Uncommon	Fatigue
Gastrointestinal disorders	
Common	Nausea

Combination with a sulphonylurea
In controlled clinical trials with the combination of vildagliptin 50 mg + a sulphonylurea, the overall incidence of withdrawals due to adverse reactions was 0.6% in the vildagliptin 50 mg + sulphonylurea vs 0% in the placebo + sulphonylurea treatment group.

In clinical trials, the incidence of hypoglycaemia when vildagliptin 50 mg once daily was added to glimepiride was 1.2% versus 0.6% for placebo + glimepiride. No severe hypoglycaemic events were reported in the vildagliptin arms.

In clinical trials, weight did not change from baseline when vildagliptin 50 mg daily was added to glimepiride (-0.1 kg and -0.4 kg for vildagliptin and placebo, respectively).

Table 2 Adverse reactions reported in patients who received Galvus 50 mg in combination with a sulphonylurea in double-blind studies (N=170)

Infections and infestations	
Very rare	Nasopharyngitis
Nervous system disorders	
Common	Tremor
Common	Headache
Common	Dizziness

Gastrointestinal disorders	
Uncommon	Constipation
General disorders and administration site conditions	
Common	Asthenia

Combination with a thiazolidinedione
In controlled clinical trials with the combination of vildagliptin 100 mg daily+ a thiazolidinedione, no withdrawal due to adverse reactions was reported in either the vildagliptin 100 mg daily + thiazolidinedione or the placebo + thiazolidinedione treatment groups.

In clinical trials, the incidence of hypoglycaemia was uncommon in patients receiving vildagliptin + pioglitazone (0.3%) but common in patients receiving placebo + pioglitazone (1.9%). No severe hypoglycaemic events were reported in the vildagliptin arms.

In the pioglitazone add-on study, the absolute weight increases with placebo, Galvus 100 mg daily were 1.4 and 2.7 kg, respectively.

The incidence of peripheral oedema when vildagliptin 100 mg daily was added to a maximum dose of background pioglitazone (45 mg once daily) was 7.0%, compared to 2.5% for background pioglitazone alone.

Table 3 Adverse reactions reported in patients who received Galvus 100 mg daily in combination with a thiazolidinedione in double-blind studies (N=158)

Nervous system disorder	
Uncommon	Headache
Uncommon	Asthenia
Metabolism and nutrition disorders	
Common	Weight increase
Vascular disorders	
Common	Oedema peripheral

In addition, in controlled monotherapy trials with vildagliptin 100 mg daily, adverse reactions reported in patients treated with vildagliptin in excess of that in patients receiving placebo are dizziness, headache, oedema peripheral, constipation, nasopharyngitis, upper respiratory tract infection and arthralgia. In these trials, the overall incidence of withdrawals due to adverse reactions was no greater for patients treated with vildagliptin at doses of 100 mg daily (0.3%) than for placebo (0.6%) or comparators (0.9%).

In comparative controlled monotherapy studies, hypoglycaemia was uncommon, reported in 0.4% (7 of 1,855) of patients treated with vildagliptin 100 mg daily compared to 0.2% (2 of 1,082) of patients in the groups treated with an active comparator or placebo, with no serious or severe events reported.

In controlled monotherapy trials of up to one year in duration, the incidence of ALT or AST elevations > 3x ULN (classified as present on at least 2 consecutive measurements or at the final on-treatment visit) was 0.3%, 0.9% and 0.3% for vildagliptin 50 mg once daily, vildagliptin 100 mg daily (administered as single and divided doses) and placebo, respectively. These elevations in transaminases were generally asymptomatic, non-progressive in nature and not associated with cholestasis or jaundice.

In clinical trials, weight did not change from baseline when vildagliptin 100 mg daily was administered as monotherapy (-0.3 kg and -1.3 kg for vildagliptin and placebo, respectively).

4.9 Overdose

Information regarding overdose with vildagliptin is limited.

Information on the likely symptoms of overdose was taken from a rising dose tolerability study in healthy subjects given Galvus for 10 days. At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paraesthesia, fever, oedema and a transient increase in lipase levels. At 600 mg, one subject experienced oedema of the feet and hands, and increases in creatine phosphokinase (CPK), aspartate aminotransferase (AST), C-reactive protein (CRP) and myoglobin levels. Three other subjects experienced oedema of the feet, with paraesthesia in two cases. All symptoms and laboratory abnormalities resolved without treatment after discontinuation of the study medicinal product.

Management
In the event of an overdose, supportive management is recommended. Vildagliptin cannot be removed by haemodialysis. However, the major hydrolysis metabolite (LAY 151) can be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dipeptidyl peptidase 4 (DPP-4) inhibitors, ATC code: A10BH02

Vildagliptin, a member of the islet enhancer class, is a potent and selective DPP-4 inhibitor.

The administration of vildagliptin results in a rapid and complete inhibition of DPP-4 activity, resulting in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide).

By increasing the endogenous levels of these incretin hormones, vildagliptin enhances the sensitivity of beta cells to glucose, resulting in improved glucose-dependent insulin secretion. Treatment with vildagliptin 50-100 mg daily in patients with type 2 diabetes significantly improved markers of beta cell function including HOMA-β (Homeostasis Model Assessment–β), proinsulin to insulin ratio and measures of beta cell responsiveness from the frequently-sampled meal tolerance test. In non-diabetic (normal glycaemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.

By increasing endogenous GLP-1 levels, vildagliptin also enhances the sensitivity of alpha cells to glucose, resulting in more glucose-appropriate glucagon secretion.

The enhanced increase in the insulin/glucagon ratio during hyperglycaemia due to increased incretin hormone levels results in a decrease in fasting and postprandial hepatic glucose production, leading to reduced glycaemia.

The known effect of increased GLP-1 levels delaying gastric emptying is not observed with vildagliptin treatment.

A total of 5,759 patients with type 2 diabetes participated in 13 double-blind placebo- or active-controlled clinical trials of at least 12-weeks' treatment duration. In these studies, vildagliptin was administered to 3,784 patients at daily doses of 50 mg (once daily) or 100 mg (50 mg twice daily or 100 mg once daily). The number of male and female patients receiving vildagliptin 50 mg once daily or 100 mg daily was 2,069 and 1,715, respectively. The number of patients receiving vildagliptin 50 mg once daily or 100 mg daily who were $\geq$ 65 years of age was 664 and 121 of the patients were $\geq$ 75 years of age. In these trials, vildagliptin was administered as monotherapy in drug-naïve patients with type 2 diabetes or in combination in patients not adequately controlled by other antidiabetic medicinal products.

Overall, vildagliptin improved glycaemic control when given as monotherapy or when used in combination with metformin, a sulphonylurea, and a thiazolidinedione, as measured by clinically relevant reductions in HbA_{1c} from baseline at study endpoint (see Table 4).

In clinical trials, the magnitude of HbA_{1c} reductions with vildagliptin was greater in patients with higher baseline HbA_{1c}.

In a 52-week double-blind controlled trial, vildagliptin (100 mg/day) reduced baseline HbA_{1c} by -1% compared to -1.6% for metformin (titrated to 2 g/day) statistical non-inferiority was not achieved. Patients treated with vildagliptin reported significantly lower incidences of gastrointestinal adverse reactions versus those treated with metformin.

In a 24-week double-blind controlled trial, vildagliptin (100 mg day) was compared to rosiglitazone (8 mg once daily). Mean reductions were -1.20% with vildagliptin and -1.38% with rosiglitazone in patients with mean baseline HbA_{1c} of 8.7%. Patients receiving rosiglitazone experienced a mean increase in weight (+1.6 kg) while those receiving vildagliptin experienced no weight gain (-0.3 kg). The incidence of peripheral oedema was lower in the vildagliptin group than in the rosiglitazone group (2.1% vs. 4.1% respectively).

Table 4 Key efficacy results of vildagliptin in placebo-controlled monotherapy trials and in add-on combination therapy trials (primary efficacy ITT population)

Monotherapy placebo controlled studies	**Mean baseline HbA_{1c} (%)**	**Mean change from baseline in HbA_{1c} (%) at week 24**	**Placebo-corrected mean change in HbA_{1c} (%) at week 24 (95%CI)**
Study 2301: Vildagliptin 50 mg twice daily (N=90)	8.6	-0.8	-0.5* (-0.8, -0.1)
Study 2301: Vildagliptin 100 mg once daily (N=92)	8.4	-0.9	-0.6* (-0.9, -0.2)
Study 2384: Vildagliptin 50 mg twice daily (N=79)	8.4	-0.7	-0.7* (-1.1, -0.4)
Study 2384: Vildagliptin 100 mg once daily (N=89)	8.3	-0.8	-0.9* (-1.2, -0.5)
		* p< 0.05 for comparison versus placebo	
Add-on / Combination studies			
Vildagliptin 100 mg daily + metformin (N=143)	8.4	-0.9	-1.1* (-1.4, -0.8)
Vildagliptin 50 mg daily + glimepiride (N=132)	8.5	-0.6	-0.6* (-0.9, -0.4)
Vildagliptin 100 mg daily + pioglitazone (N=136)	8.7	-1.0	-0.7* (-0.9, -0.4)
		* p< 0.05 for comparison versus placebo + comparator	

5.2 Pharmacokinetic properties

Absorption

Following oral administration in the fasting state, vildagliptin is rapidly absorbed, with peak plasma concentrations observed at 1.7 hours. Food slightly delays the time to peak plasma concentration to 2.5 hours, but does not alter the overall exposure (AUC). Administration of vildagliptin with food resulted in a decreased C_{max} (19%). However, the magnitude of change is not clinically significant, so that Galvus can be given with or without food. The absolute bioavailability is 85%.

Distribution